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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/493,891	01/28/2000	Wallace A. Longton	LEH-35B-98	2793

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EXAMINER	
MAIER, LEIGH C	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 06/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/493,891	LONGTON ET AL.	
	Examiner	Art Unit	
	Leigh C. Maier	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-14 and 16-23* is/are pending in the application.

4a) Of the above claim(s) *10-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-9 and 16-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.0.0.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 22, 2005 has been entered.

The original restriction requirement has been reconsidered, and claims 1 and 2 have been rejoined with claims 3, 5-9, and newly added claims 16-23 for examination. Claims 10-14 remain withdrawn as being drawn to a non-elected invention.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Any objection or rejection not expressly repeated has been withdrawn.

Claim Rejections - 35 USC § 112

Claims 1, 2, and 16-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 comprises a carboxymethyl cellulose (CMC) compound that is depicted in a structural formula. As drawn, it appears to depict a CMC having a d.s. of exactly 1, with carboxymethylation only at position 2, and 100% lactonization. It is not clear if this structure is

meant to be (1) exactly representative; (2) more of a schematic drawing of a CMC having DP of 500 to 2000 and some degree of lactonization; or (3) something else.

Claim 2 recites "wherein "n" is an 15 integer from 1000 to 15000." It is not clear what is meant by "an 15 integer." Furthermore, the range of "from 1000 to 15000" does not properly depend from claim 1 which recites the range of 500 to 2000.

Claim 16 is a product-by-process claim wherein the polysaccharide product is "free of residual chemical activators and promoters." At page 5, 2nd full paragraph, the specification gives some examples of "chemical activators" and "promoters," but does not describe the full range of what is to be excluded from the products set forth in claims 16-22. Thus, one of ordinary skill would not be apprised of the metes and bounds of the claims.

Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As discussed above, it is not clear exactly what is meant by the structural formula depicted in claim 1. Some possible meanings were offered, including option (1) wherein the structure is meant to be exactly representative. If this is the case, the specification does not appear to be enabling for the preparation of such a compound. As is known in the art, typical methods of preparing CMC results in a non-uniform distribution of carboxymethyl substituents along the polymer chain. This is typical for carboxymethylated polysaccharides in general. See also HEINDEL at page 99, 2nd paragraph under "Results and Discussion."

HEINZE teaches a method for the preparation of 2,3-O-CMC by first selectively protecting at position 6, followed by carboxymethylation at positions 2 and 3. However, lactonization of this product would not result in the one depicted in the claim. This would require perfectly selective de-carboxymethylation at position 3 followed by complete lactonization.

The specification does not appear to contemplate much less describe such a process. There is no discussion of carboxymethylation at all, as Applicant appears to use commercially available products as starting materials. Although the level of skill would be expected to be high, and the art fairly predictable, the difficulty of selective and complete carboxymethylation at position 2 would be quite high. Therefore, one of ordinary skill would require undue experimentation to prepare such a product.

Claim Rejections - 35 USC § 102

Claim 9 is rejected under 35 U.S.C. 102(a) as being anticipated by MARTEY et al (CAPLUS abstract 1998:529836, 1998). Newly added claims 16 and 17 are included in this rejection.

Applicant's arguments filed March 22, 2005 have been fully considered but they are not persuasive.

MARTEY teaches a CM-cellulose lactone, as discussed in previous Office actions. Citing MPEP 2121.01, Applicant argues that a properly applied reference must enable one of ordinary skill to prepare the compounds that are disclosed. The examiner agrees. However, MPEP 2121.02 addresses this point further: A reference is presumed operable until Applicant provides *facts* rebutting the presumption of operatibility. *In re Sasse*, 629 F.2d 675, 207 USPQ 107

(CCPA 1980). (Emphasis added) Arguments supplied are not evidence. Therefore, Applicant must provide evidence showing that a process for making was not known at the time of the invention. A persuasive argument to that effect appears unlikely given that references describing the preparation of polysaccharide lactones have been discussed at length in the course of this prosecution. The examiner maintains that the compound is disclosed and thus anticipates this claim.

Claim 9 is again rejected under 35 U.S.C. 102(b) as being anticipated by AKANUMA et al (J. Biochem., 1978), as set forth in the previous Office action.

Applicant's arguments filed March 22, 2005 have been fully considered but they are not persuasive.

Applicant contends that the reference does not provide any confirmation of lactone formation from CM-cellulose. However, the reference clearly states that "CM-cellulose, in place of CM-Sephadex in Steps I and II, was also converted to its hydrazide derivative and elementary analysis showed a conversion similar to that obtained with CM-Sephadex." See page 1360 under "Applicability of Hydrazide Synthesis via the *Lactone* Derivative." Emphasis added.

Furthermore, "Step I" is explicitly described as "lactone formation." While the reference may not provide the analytical data for the CM-cellulose lactone, all indications are that this derivative was indeed prepared. Since the Office does not have the facilities for preparing the claimed materials and comparing them with prior art inventions, the burden is on Applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d

67, 205 USPQ 594 (CCPA 1980). Therefore, if Applicant maintains the position that the reference does not disclose this derivative; the burden is on Applicant to show that this process (Step I) does *not* result in a lactone.

Applicant further notes that claim 3 has been amended to recite polysaccharide carboxylic acids, so that the resulting products are not described by the reference. The amendment is noted, but examiner does not understand this argument. Claim 9 is a product-by-process claim for a lactone product prepared by the process of claim 3, wherein the polysaccharide substrates are limited to ones including carboxymethyl cellulose, a.k.a., CM-cellulose, the substrate used in the reference.

Claim Rejections - 35 USC § 103

Claims 1-3, 5, 6, 9, 16, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over HEINDEL et al (Bioconjugate Chem., 1994) in view of DIENER et al (US 4,415,552) and further in view of either of (1) AKANUMA et al (J. Biochem., 1978) or (2) MARTEY et al (CAPLUS abstract 1998:529836, 1998).

HEINDEL teaches the preparation of CM-dextran lactone thermal dehydration of the acid form of CM-dextran in anhydrous, non-nucleophilic solvents, such as toluene, diglymes, or acetonitrile at reflux temperature. See "Experimental Procedures" at pages 98 and 99. The reaction can be monitored by IR analysis. The reference further teaches that the lactone products are active species that are useful for the attachment of pharmaceuticals to the polysaccharide. The process has the advantage of not needing chemical activators, such as a carbodiimide that may lead to N-acylurea residues and leave residual impurities. See the first three paragraphs and

last paragraph of the reference. The reference does not teach the preparation of CM-cellulose lactone.

The attachment of small molecules to polysaccharide carriers is a concept that is well known in the art. DIENER teaches that CMC having a MW of about 250 kDa (DP of about 1100) has utility for the attachment of allergens and haptens. See abstract and col 5, lines 6-11. The reference teaches the preparation of CMC conjugates using a carbodiimide activator. See example 1.

AKANUMA and MARTEY teach as set forth above. From either of these references it is known that it is possible to prepare a CM-cellulose lactone and would therefore lead one of ordinary skill to the conclusion that this process could be used for carboxylated polysaccharides generally with a reasonable expectation of success.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare CM-cellulose lactone by the method of HEINDEL for the art-disclosed utility. One of ordinary skill would be motivated to use this method to avoid the disadvantages of using chemical activators, as discussed in HEINDEL. Both AKANUMA and MARTEY disclose the CM-cellulose lactone, so one of ordinary skill would know that is it possible to prepare polysaccharide lactones. Therefore, the artisan would reasonably expect success in using the HEINDEL process to prepare this product. It would be further obvious to prepare the product having a degree of substitution as set forth in claims 1 and 2 because DIENER had taught that this molecular weight was useful in preparing allergen-CMC conjugates.

The reference is silent regarding whether or not the starting material is in the form of a fine powder. However, if necessary, it would be further obvious to prepare it in such a form to facilitate faster dissolution by soluble reactants or provide more reactive surface area in the case of suspended reactants. The reference is also silent regarding the presence of carboxylate salts. However, it would be obvious to one having ordinary skill to maximize the active acid form and minimize the amount of inactive salt. Finally it would be obvious to one of ordinary skill to select any of the solvents disclosed for the process. Applicant has not demonstrated any criticality in any particular polysaccharide/solvent pair.

It appears to be Applicant's position that one of ordinary skill would consider dextran to be a special case because it is "virtually unique among polysaccharides in that it is very water soluble" and therefore would assume that results for dextran could not be extrapolated to other polysaccharides. The examiner fails to see how dextran's water-solubility is relevant to the instant process. First of all, it has been noted before, neither of these polysaccharides, *per se*, is a substrate for this reaction. The starting material in this process is the *carboxymethylated* polysaccharide. CM-cellulose, for example, is well known to be water-soluble. Moreover, the reaction is conducted in an *anhydrous* organic solvent.

One of ordinary skill would be aware of the fact that dextran is 1,6-linked and cellulose is 1,4-linked. The 1,6-linking structure allows for more possibilities of formation of a CM substituent adjacent to a free hydroxyl allowing formation of a 6-membered lactone. The artisan would therefore expect slower lactonization in a 1,4-linked polysaccharide. However, both AKANUMA and MARTEY had demonstrated that CM-cellulose is capable of undergoing lactonization. It would be within the scope of the artisan to monitor the reaction as directed by

HEINDEL and adjust the reaction time accordingly. With respect to what was known at the time about lactone formation, it is noteworthy that HEINDEL compares the analytical data for CM-dextran lactone with that reported by AKANUMA as supporting lactone formation in the CM-dextran product. See 1st paragraph under "Results and Discussion."

Claims 3, 5, 9, 16, 20, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over HEINDEL et al (Bioconjugate Chem., 1994) in view of WEINSHENKER (US 5,068,227) and further in view of either of (1) AKANUMA et al (J. Biochem., 1978) or (2) MARTEY et al (CAPLUS abstract 1998:529836, 1998).

HEINDEL teaches as set forth above. The reference does not teach the use of cyclodextrins.

WEINSHENKER teaches that the covalent attachment of biorecognition molecules to cyclodextrins. See abstract and col 4. The cyclodextrins are activated by the preparation of carboxy- or carboxymethyl derivatives. See col 3, lines 25-46.

AKANUMA and MARTEY teach as set forth above.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare CM-cyclodextrin lactone by the method of HEINDEL for the art-disclosed utility for the advantages discussed above. Cyclodextrin is a 1,4-linked polysaccharide, so a CM substituent at position 2 or 3 would be expected to lactonize under these conditions, similar to CM-cellulose. Therefore, the artisan would reasonably expect success in using the HEINDEL process to prepare this product.

Claims 3, 5, 9,16, 21, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over HEINDEL et al (Bioconjugate Chem., 1994) in view of ELSON (US 5,888,988) and further in view of either of (1) AKANUMA et al (J. Biochem., 1978) or (2) MARTEY et al (CAPLUS abstract 1998:529836, 1998).

HEINDEL teaches as set forth above. The reference does not teach the use of chitosan.

ELSON teaches that CM-chitosan has utility for the covalent attachment of therapeutically active compounds. Conjugates are prepared by carbodiimide-facilitated coupling. See abstract and example 3.

AKANUMA and MARTEY teach as set forth above.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare CM-chitosan lactone by the method of HEINDEL for the art-disclosed utility for the advantages discussed above. Cyclodextrin is a 1,4-linked polysaccharide, so a CM substituent at position 2 (N) would be expected to lactonize under these conditions, similar to CMC. Therefore, the artisan would reasonably expect success in using the HEINDEL process to prepare this product.

Claims 3, 5, 8, 9, 16, 19, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over HEINDEL et al (Bioconjugate Chem., 1994) in view of HATTORI et al (J. Agric. Food Chem., 1995) and further in view of either of (1) AKANUMA et al (J. Biochem., 1978) or (2) MARTEY et al (CAPLUS abstract 1998:529836, 1998).

HEINDEL teaches as set forth above. The reference does not teach the use of CM-starch.

HATTORI teaches the covalent attachment of a protein to CM-starch via carbodiimide coupling. See paragraph bridging pp 2007-8.

AKANUMA and MARTEY teach as set forth above.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare CM-starch lactone by the method of HEINDEL as an activated species to prepare the starch/protein conjugate and avoid the disadvantages of a carbodiimide coupling. Starch is a 1,4-linked polysaccharide, so a CM substituent at position 2 or 3 would be expected to lactonize under these conditions, similar to CMC. Therefore, the artisan would reasonably expect success in using the HEINDEL process to prepare this product. It would be further obvious to select any of the solvents taught by HEINDEL. Applicant has not demonstrated any criticality in any particular polysaccharide/solvent pair.

Claims 3, 5, 7, 9, 16, 18, 22, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over HEINDEL et al (Bioconjugate Chem., 1994) in view of MILL et al (US 4,003,972) and further in view of STREITWIESER et al (Introduction to Organic Chemistry, 1976).

HEINDEL teaches as set forth above. The reference does not teach the use of pectin or other carboxy-polysaccharides to prepare a lactone.

MILL teaches that acidic polysaccharides, such as pectin/pectic acid and celluronic acid (carboxycellulose), have utility for the preparation of conjugates comprising a variety or organic substances. See col 1, lines 25-27 and the paragraph bridging col 1-2. These conjugates are prepared using a carbodiimide coupling agent. See col 2, lines 26-35 and examples.

STREITWIESER teaches that lactone formation is particularly favored when it results in a 5- or 6-membered ring. See pp 685-687, section B. 1.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use the process of HEINDEL to prepare lactones of the acidic polysaccharides taught by MILL, the ones specifically cited or similar ones, such as carboxy-starch, for the advantages discussed above. The artisan would be motivated to prepare a lactone as an active species to prepare conjugates taught in the reference. One of ordinary skill would reasonably expect success in the preparation of a lactone with these polysaccharides because the reaction of the acid at position 6 and the hydroxyl at position 3 would result in a 5-membered ring. It would be obvious to one of ordinary skill to select any of the solvents disclosed for the process. Applicant has not demonstrated any criticality in any particular polysaccharide/solvent pair.

Examiner's hours, phone & fax numbers

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (571) 272-0656. The examiner can normally be reached on Tuesday, Thursday, and Friday 7:00 to 3:30 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson (571) 272-0661, may be contacted. The fax number for Group 1600, Art Unit 1623 is (703) 872-9306.

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Leigh C. Maier

Leigh C. Maier
Primary Examiner
May 19, 2005